Skeletogenic Neural Crest Cells in Embryonic Development and Adult Regeneration of the Jaw

Grant Award Details

Skeletogenic Neural Crest Cells in Embryonic Development and Adult Regeneration of the Jaw

Grant Type: New Faculty II

Grant Number: RN2-00916

Project Objective: The overall objective of this project is to gain new insights into the mechanisms by which the neural crest contributes to the jaw skeleton of the zebrafish, how regeneration of the fish's jaw skeleton occurs, and to use these insights to develop protocols for the direct conversion of mammalian fibroblasts into neural crest derivatives, first in mouse and then in human.

Investigator:

Name:	Gage DeKoeyer Crump
Institution:	University of Southern California
Type:	PI

Disease Focus: Bone or Cartilage Disease, Trauma

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $2,247,403

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Grant Application Details

Application Title: Skeletogenic Neural Crest Cells in Embryonic Development and Adult Regeneration of the Jaw

Public Abstract:

The goal of this proposal is to develop cell-based therapies that lead to the better healing of traumatic head injuries. Our first strategy will be to use genetics and embryology in zebrafish to identify factors that can convert human embryonic stem cells into replacement skeleton for the head and face. Remarkably, the genes and mechanisms that control the development of the head are nearly identical between fish and man. As zebrafish develop rapidly and can be grown in large numbers, a growing number of researchers are using zebrafish to study how and when cells decide to make a specific type of tissue – such as muscle, neurons, and skeleton - in the vertebrate embryo. Recently, we have isolated two new zebrafish mutants that completely lack the head skeleton. By studying these mutants, we hope to identify the cellular origins and genes that make head skeletal precursors in the embryo. These genes will then be tested for their ability to drive human embryonic stem cells along a head skeletal lineage. Our second strategy will be to test whether a population of cells, similar to the one that makes the head skeleton in the embryo, exists in the adult face. We have found that adult zebrafish have the extraordinary ability to regenerate most of their lower jaw following amputation. In this proposal, we use sophisticated imaging and transgenic approaches to identify potential adult stem cells that can give rise to new head skeleton in response to injury. Traumatic injuries to the face are common, and treatment typically involves grafting skeleton from other parts of the patient to the injury site. Unfortunately, the amount of skeleton available for grafts is in short supply, and surgeries often result in facial disfigurement that causes psychological suffering for the patient for years to come. Here we propose two better treatments that would lead to more efficient healing and less scarring. The first treatment would be to differentiate human embryonic stem cells, a potentially limitless resource, into skeletal precursors that can be grafted into the head injury site. By understanding the common pathways by which head skeletal cells are specified in the zebrafish embryo and human embryonic stem cells, we will be able to generate skeletal replacement cells in large quantities in cell culture. The second treatment would be to stimulate adult stem cells already in the face to regenerate the injured head skeleton. If successful, our experiments on zebrafish jaw regeneration will allow us to devise strategies to augment the natural skeletal repair mechanisms of humans.

Statement of Benefit to California: Traumatic injuries to the head, such as those caused by car accidents and gunshot wounds, are commonly seen in emergency rooms throughout California. Current treatments for severe injuries of the head skeleton involve either grafting skeleton from another part of the body to the injury site or, in cases where there is not sufficient skeleton available for grafts, implanting metal plates. Although these operations save lives, they often result in facial disfigurement that causes psychological suffering for the patient for years to come. For this reason, there is enormous interest in cell-based skeletal replacement therapies that will heal the face without leaving disfiguring scars. Remarkably, the genes and mechanisms that control the development of the head are nearly identical between fish and man. Thus, we are using the zebrafish embryo to rapidly identify factors that can make head skeletal precursors, and then asking if these same factors can instruct human embryonic stem cells to form skeletal replacement cells. In addition, we have found that adult zebrafish have the extraordinary ability to regenerate most of their lower jaw following amputation, and we will use sophisticated imaging and transgenic approaches to identify potential adult stem cells that can regenerate the face. The successful completion of these experiments would allow us to both generate unlimited amounts of head skeletal precursors for facial repair and stimulate latent skeletal repair mechanisms. The combination of these approaches will lead to therapies that promote a more natural healing of the face, thus allowing Californians to eventually resume normal lives after catastrophic accidents.
